Claims

1. A soluble polypeptide comprising, in sequence, one to four short consensus repeats (SCR) selected from SCR 1, 2, 3 and 4 of long homologous repeat A (LHR-A) as the only structurally and functionally intact SCR domains of CR1 and including at least SCR3, in which one or more of the native amino acids are substituted with the following: Val 4, Asp 19, Ser 53, Lys 57, Ala 74, Asp 79, Arg 84, Pro 91, Asn 109, Lys 116, Val 119, Ala 132, Thr 137, Ile 139, Ser 140, Tyr 143, His 153, Leu 156, Arg 159, Lys 161, Lys 177, Gly 230, Ser 235, His 236.
(Numbering is from glutamine as residue 1 of mature CR1. The amino-acid indicated is that which replaces the CR1 residue at the position specified.)

2. A polypeptide according to claim 1 which comprises, in sequence, SCR 1, 2, 3 and 4 of LHR-A or SCR 1, 2 and 3 of LHR-A as the only structurally and functionally intact SCR domains of CR1.

3. A polypeptide according to claim 1 or 2 comprising the native interdomain sequences in CR1 optionally substituted with the corresponding predicted aminoacids in the CR1-like sequence, namely Lys59 and/or Ile124. (Numbering is from glutamine as residue 1 of mature CR1. The amino-acid indicated is that which replaces the CR1 residue at the position specified.)

4. A polypeptide according to claim 2 or 3 of formula (I):

$$NH_2\text{-}V^1\text{-SCR1-}W^1\text{-SCR2-}X^1\text{-SCR3-}Y^1\text{-OH} \qquad (I)$$

in which SCR1 represents residues 2-58 of mature CR1, SCR2 represents residues 63-120 of mature CR1, SCR3 represents residues 125-191 of mature CR1, and containing at least one of the substitutions as aforesaid and V^1, W^1, X^1 and Y^1 represent bonds or short linking sequences of amino acids, preferably 1 to 5 residues in length and which are preferably derived from native interdomain sequences in CR1, optionally substituted as defined in claim 3.

5. A polypeptide according to claim 4 wherein W^1, X^1 and Y^1 represent residues 59-62, 121-124 and 192-196, respectively, of mature CR1, optionally substituted as defined in claim 3, and V^1 represents residue 1 of mature CR1 optionally linked via its N-terminus to methionine.

6. A polypeptide according to claim 2 or 3 of formula (II):

$$NH_2\text{-}V^2\text{-SCR1-}W^2\text{-SCR2-}X^2\text{-SCR3-}Y^2\text{-SCR4-}Z^2\text{OH} \qquad (II)$$

in which SCR1, SCR2 and SCR3 are as hereinbefore defined, SCR4 represents residues 197-252 of mature CR1 and containing at least one of the substitutions as aforesaid. and V^2, W^2, X^2, Y^2 and Z^2 represent bonds or short linking sequences of amino acids, preferably 1 to 5 residues in length and which are preferably derived from native interdomain sequences in CR1, optionally substituted as defined in claim 3.

7. A polypeptide according to claim 6 wherein W^2, X^2, Y^2 and Z^2 represent residues 59-62, 121-124, 192-196, and residues 253 respectively, of mature CR1, optionally substituted as defined in claim 3, and V^2 represents residue 1 of mature CR1 optionally linked via its N-terminus to methionine.

8. A polypeptide according to claim 1 or 3 of formula (III):

$$NH_2\text{-}X^3\text{-}SCR3\text{-}Y^3\text{-}OH \qquad (III)$$

in which SCR3 is as hereinbefore defined, containing at least one of the substitutions as aforesaid, and in a preferred embodiment, all those of Sequence Group 1 aforesaid, and in a preferred embodiment, all those of Sequence Group 1, namely: A132, T137, I139, S140, Y143, H153, L156, R159, K161, K177, and X^3 and Y^3, and X^3 and Y^3 represent bonds or short linking sequences of amino acids, preferably 1 to 5 residues in length and which are preferably derived from native interdomain sequences in CR1, optionally substituted as defined in claim 3.

9. A polypeptide according to claim 8 wherein X^3 represents amino acids 122-124 of mature CR1, optionally substituted as defined in claim 3, optionally linked to methionine at its N-terminus and Y^4 represents amino acids 192-196 of mature CR1.

10. A polypeptide according to claim 1 or 3 of formula (IV):

$$NH_2\text{-}X^4\text{-}SCR3\text{-}Y^4\text{-}SCR4\text{-}Z^4\text{-}OH \qquad (IV)$$

in which SCR3 and SCR4 are as hereinbefore defined containing at least one of the substitutions as aforesaid and X^4, Y^4 and Z^4 represent bonds or short linking sequences of amino acids, preferably 1 to 5 residues in length and which are preferably derived from native interdomain sequences in CR1, optionally substituted as defined in claim 3.

11. A polypeptide according to claim 10 wherein X^4 represents amino acids 122-124 of mature CR1, optionally substituted as defined in claim 3, optionally linked to methionine at its N-terminus and Y^4 and Z^4 represent amino acids 192-196 and 253 respectively of mature CR1.

12. A polypeptide according to any preceding claim wherein the SCR3 domain is substituted with all ten residues found in the corresponding pseudogene sequence, namely (in single letter code):

A132, T137, I139, S140, Y143, H153, L156, R159, K161, K177 (Sequence Group 1)

and the remaining domains have the sequence of mature CR1.

13. A polypeptide according to claim 1 selected from SEQ ID NOs: 1, 9, 11, 13, 15, 17, , 19, 21, 23, 25, 27 and 29.

14. A soluble derivative of the soluble polypeptide of any preceding claim, said derivative comprising two or more heterologous membrane binding elements with low membrane affinity covalently associated with the polypeptide which elements are capable

of interacting independently and with thermodynamic additivity with components of cellular membranes exposed to extracellular fluids.

15. A derivative according to claim 14 compring two to eight membrane binding elements selected from: fatty acid derivatives; ligands of known integral membrane proteins; sequences derived from the complementarity-determining region of monoclonal antibodies raised against epitopes of membrane proteins; membrane binding sequences identified through screening of random chemical libraries.

16. A derivative according to claim 14 or 15 having the following structure:

$[P]-\{L-[W]\}_n-X$

in which:

P is the soluble polypeptide,

each **L** is independently a flexible linker group,

each **W** is independently a peptidic membrane binding element,

n is an integer of 1 or more and

X is a peptidic or non-peptidic membrane-binding entity which may be covalently linked to any **W**.

17. A polypeptide derivative which is SEQ ID NO: 34, 49 or 51

18. The polypeptide portion of a derivative according to any of claims 14 to 17, wherein the polypeptide portion is SEQ ID NO: 31, 36, 50, 54 or 57.

19. A process for preparing a polypeptide according to any of claims 1 to 13 which process comprises expressing DNA encoding said polypeptide in a recombinant host cell and recovering the product.

20. A DNA polymer comprising a nucleotide sequence that encodes the polypeptide of any of claims 1 to 13, or 18.

21. A DNA polymer according to claim 20 selected from SEQ ID NOs: 1,10, 12, 14, 16, 18, 20, 22, 24, 26, 28, or 30,

22. A replicable expression vector capable, in the host cell, of expressing the DNA polymer of claim 20 or 21.

23. A host cell transformed with a replicable expression vector of claim 22.

24. A process for preparing a derivative according to any of claims 14 to 17 which process comprises expressing DNA encoding the polypeptide portion of said derivative in a recombinant host cell and recovering the product and thereafter post translationally modifying the polypeptide to chemically introduce membrane binding elements.

25. A pharmaceutical composition comprising a therapeutically effective amount of a polypeptide or derivative of any of claims 1 to17, and a pharmaceutically acceptable carrier or excipient.

26. A method of treating a disease or disorder associated with inflammation or inappropriate complement activation comprising administering to a subject in need of such treatment a therapeutically effective amount of a polypeptide or derivative of any of claims 1 to17.

27. The use of a polypeptide or derivative of any of claims 1 to17 in the manufacture of a medicament for the treatment of a disease or disorder associated with inflammation or inappropriate complement activation.

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AMENDED SHEET